UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/540,460	01/17/2006	David Alland	UMD-0112	4649

46046 7590 09/04/2008

LICATA & TYRRELL P.C.
66 EAST MAIN STREET
MARLTON, NJ 08053

EXAMINER
MYERS, CARLA J

ART UNIT	PAPER NUMBER
1634	

NOTIFICATION DATE	DELIVERY MODE
09/04/2008	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

poreilly@licataandtyrrell.com

Office Action Summary	Application No.	Applicant(s)	
	10/540,460	ALLAND ET AL.	
	Examiner	Art Unit	
	Carla Myers	1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on *6/5/08*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-7* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-7* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. This action is in response to the amendment filed June 5, 2008. Applicant's arguments have been fully considered but are not persuasive to overcome all grounds of rejection. All rejections not reiterated herein are hereby withdrawn. In particular, the previous rejections of the claims under 35 USC 112, second paragraph and under 35 USC 102 and 103 are withdrawn in view of the amendments to the claims. However, new grounds of rejection necessitated by Applicant's amendments to the claims are set forth below. This action is made final.

Specification

2. The amendment filed June 5, 2008 is objected to under 35 U.S.C. 132(a) because it introduces new matter into the disclosure. 35 U.S.C. 132(a) states that no amendment shall introduce new matter into the disclosure of the invention. The added material which is not supported by the original disclosure is as follows:

The amendment states that the present application is the National Stage of PCT/US2003/041136, which claims the benefit of U.S. Provisional Application 60/437,165, "each of which are herein incorporated by reference." However, when a benefit claim is submitted after the filing of an application, the reference to the prior application cannot include an incorporation-by-reference to the prior application. An incorporation-by-benefit statement added after an application's filing date is not proper because no new matter can be added to an application after its filing date. See Dart Industries v. Banner, 636 F. 2d 684, 207 USPQ 273 (C.A.D.C. 1980).

Further, the amendment refers to "PCT/US2003/041136", whereas the correct International Application No. is PCT/US03/41136.

Applicant is required to cancel the new matter in the reply to this Office Action.

New Grounds of Rejection

Claim Rejections - 35 USC § 112 second paragraph

3. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-7 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 1-7 are indefinite over the recitation of “primer-template matches.” This phrase is not clearly defined in the specification and there is no art recognized definition for this phrase. It is unclear as to what constitutes "primer-template matches" and the distinction between reactions containing primer-template matches and reactions containing the amplified product of the short amplicon.

Claims 2-4 are indefinite over the recitation of "the 30 to 90 base pair long amplicon of the nucleic acid sequence" (claim 2) because this phrase lacks proper antecedent basis. While the claims previously refer to “a short amplicon consisting of 30 to 90 base pairs of a nucleic acid molecule,” the claims do not previously refer to an amplicon of a "nucleic acid sequence." This rejection may be overcome by amendment

of the claims to recite "the 30 to 90 base pair long amplicon of the nucleic acid molecule."

Claim Rejections - 35 USC § 112 – New Matter

4. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-7 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The specification as originally filed does not appear to provide basis for the concept of comparing the efficiency or threshold cycle or amount of amplified product in a reaction containing the short amplicon of 30 to 90 base pairs with any reaction "containing primer-template matches."

In the reply of June 5, 2008, Applicants point to pages 7, lines 34 to page 8 line 4, Examples 3 and 7 and Figure 1 as providing support for these amendments. As amended, the claims encompass a comparison with a reaction containing any primer and template which share any degree of matches. However, the cited teachings in the specification provide support only for the concept of a comparison step with a reaction containing a hairpin primer and a template which are "perfectly matched" (i.e., fully complementary). In particular, page 7, lines 33-35 states that "hairpin primers that are

perfectly matched to their targets formed more stable biomolecular primer-target hybrids." In Examples 3 and 7 (pages 15 and 18), a comparison step is performed between reactions containing hairpin primers and wildtype (no mismatches) and mutant (presence of a mismatch) templates. Similarly, Figure 1 depicts two reactions, each containing a hairpin primer, wherein one reaction includes a template that has no mismatches with the hairpin primer, and the second reaction includes a template that has one mismatch with the hairpin primer. The cited passages do not, however, provide support for the concept of a comparison step with a reaction containing any type of primer and in which the template has any number of matches with the primer, as is encompassed by the claims.

Claim Rejections - 35 USC § 103

5. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to

consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1-6 are rejected under 35 U.S.C. 103(a) as being unpatentable over Nazarenko et al (U.S. Patent No. 6,090,552, 7/18/2000) as evidenced by GenBank Accession No. NM_000025 (April 1999), in view of Matsuzaki (U.S. Patent No. 6,333,179; cited in the IDS of June 22, 2005), Metallinos (U.S. Patent No. 6,372,900, cited in the IDS of June 22, 2005), and Lopez (U.S. Patent No. 6,514,698).

Nazarenko (see column 27; and 52-54, Example 10) teaches a method for detecting the presence of a single nucleotide polymorphism or a mutation in a target nucleic acid in an organism wherein the method comprises: (i) amplifying a nucleic acid sequence using a hairpin primer, wherein the hairpin primer terminates at a polymorphic position, such that the 3' nucleotide of the hairpin primer is located at the position of the single nucleotide polymorphism or mutation; and (ii) measuring the amount of amplification product wherein a decrease in the amplification product is indicative of the presence of a polymorphism or mutation (i.e., a mismatch between the hairpin primer and the target nucleic acid). Nazarenko (column 27) teaches that in the method of allele-specific PCR, "(u)nder the appropriate reaction conditions, the target DNA is not amplified if there is a base mismatch."

Regarding the recitation in the claims that the method is one which amplifies a 30 to 90 base pair nucleic acid molecule of an organism, the method exemplified by Nazarenko results in the amplification of 101 base pairs of the B3AR (i.e., adrenergic receptor beta-3 nucleic acid / ADRB3) nucleic acid. The fact that the method of

Nazarenko results in the amplification of 101 bp of an organisms' ADRB3 nucleic acid is evidenced by the teachings of GenBank Accession No. NM_000025 wherein the nucleotide positions to which the forward and reverse primers of Nazarenko (Table 5) hybridize are disclosed. Specifically, the forward hairpin primer of Nazarenko hybridizes to nucleotides 368-387 of B3AR nucleic acids, and the reverse primer of Nazarenko hybridizes to the inverse complement of nucleotides 449-468 of B3AR, thereby generating a product containing 101bp (and thus 30 to 90bp) of an organisms' B3AR nucleic acid.

Nazarenko does not teach a method wherein the amplification product is of a length of 30 to 90bp.

However, Matsuzaki teaches that methods of PCR are more efficient when shorter length nucleic acids are amplified. Matsuzaki (col. 1, lines 43-46) states that "The yield of longer amplicons is often less than the yield of shorter amplicons because those differences in PCR amplification efficiency." Matsuzaki (Table 3, and col. 4-5) exemplifies methods of producing amplicons of 90 bp. Lopez also teaches that methods that produce short PCR products of 30-100bp provide several advantages. It is stated that "Since the PCR reaction cycle times are shortened to a few seconds, the concentrations of the amplified DNA are increased, resulting in improved signal to noise ratio" (col. 4, lines 49-54). Lopez also states that "the use of short PCR products allows for faster amplification times and improved sensitivity through stronger signals due to higher molar concentrations" (col. 14, lines 9-12). Further, Metallinos (col. 11, lines 20-

27) exemplifies methods of allele specific PCR in which the amplification products are of a length of 90 bp.

Accordingly, it would have been obvious to one of ordinary skill in the art at the time the invention was made to have modified the method of Nazarenko so as to have selected PCR primers that produced amplicons of a shorter length, and particularly of length of 30-90 bp, in order to have improved the efficiency of the PCR assay, thereby increasing the yield of the amplification product and the sensitivity of detection of a single nucleotide polymorphism or mutation.

Regarding claim 2, in the method of Nazarenko, the nucleic acid is amplified by PCR (col. 53).

Regarding claim 4, Nazarenko teaches detecting PCR amplification products at the completion of the PCR assay (col. 53-54).

Regarding claim 5, the hairpin primers exemplified by Nazarenko comprise DNA (Table 5).

Regarding claim 3, Nazarenko exemplifies methods wherein the hairpin primer comprise DNA (Table 5), but does not exemplify methods wherein the hairpin primer comprises RNA. However, Nazarenko (col. 17, lines 36-40) does teach that the hairpin primer may be DNA or RNA.

Regarding claim 6, Nazarenko (col. 53-54) exemplifies methods using allele-specific hairpin primers wherein the PCR amplification products are detected at the completion of the PCR assay, but does not exemplify methods using allele-specific hairpin primers wherein the PCR amplification products are detected using real-time

PCR. However, Nazarenko does teach that in methods in which the amplification product is formed using a hairpin primer, the amplification product can be detected by real-time PCR (see col. 43 and 48). It is stated that real-time PCR detection provides the advantages of allowing researches to perform the method in closed tubes, thereby eliminating the risk of carry-over contamination, simplifies the detection assay, and permits quantification of the amplification products over a wide dynamic range. Accordingly, it would have been obvious to one of ordinary skill in the art at the time the invention was made to have modified the method of Nazarenko so as to have detected the amplification products using real-time PCR in order to have provided an effective means for monitoring the allele-specific amplification reaction which would simply the detection method, reduce cross-contamination and allow for a highly accurate quantification of the amplification products.

6. Claim 7 is rejected under 35 U.S.C. 103(a) as being unpatentable over Nazarenko, as evidenced by GenBank Accession No. NM_000025 (April 1999), in view of Matsuzaki, Metallinos, and Lopez, and further in view of Tyagi (U.S. Patent No. 6,365,729; cited in the IDS).

The teachings of Nazarenko, Matsuzaki, Metallinos and Lopez are presented above.

Nazarenko exemplifies methods wherein the hairpin primer comprises DNA (Table 5) and teaches that the hairpin primer may also comprise RNA or may be modified in the base, sugar or phosphate backbone (co. 17, lines 36 to col. 18, line 11). However, Nazarenko does not exemplify methods wherein the hairpin primer

comprises a PNA.

Tyagi (col. 3 and 6) teaches a method of allele-specific PCR using hairpin primers. Tyagi (column 2) teaches that "if the binding of the primer in the tube to the target sequence creates a mismatched 3'-terminal nucleotide, then the primer cannot be efficiently extended by incubation with DNA polymerase. Amplification of the mismatched template is significantly delayed." Tyagi (column 6) further teaches that hairpin primers used for allele-specific PCR may contain PNAs.

Accordingly, it would have been obvious to one of ordinary skill in the art at the time the invention was made to have modified the method of Nazarenko so as to have performed the allele-specific PCR method using hairpin primers that contain PNAs in view of the well known benefits provided by PNAs of enhancing the stability of hybridization and improving the ability to distinguish between perfectly matched and mismatched sequences. Thereby, one would have been motivated to have used PNA hairpin primers in order to have provided a highly sensitive and effective method for detecting the presence of a polymorphism or mutation.

Response to Remarks

7. In the reply of June 5, 2008, Applicants traversed the previous grounds of rejection. Those arguments are addressed below to the extent that they apply to the present grounds of rejection.

The response states that the claims have been amended to recite that the short amplicon consists of 30 to 90 base pairs. It is stated that the claimed invention is distinct from that of Nazarenko which amplifies a 101 base pair nucleic acid. It is

argued that the prior art does not suggest modifying the amplicon size to 30 to 90 bases because the typical amplicon size is approximately 100 to 300 bases. Page 8, lines 4-6 are cited as teaching "To increase amplification efficiency, the size of amplicons was substantially reduced from typical size of approximately 100 to 300 bases."

These arguments have been fully considered but are not persuasive. While the specification refers to a typical amplicon size of 100 to 300 bases, this general teaching in the specification is not supported by any factual evidence. The specification does not teach, for example, that an amplicon must be approximately 100 to 300 bases or that the prior art suggests that amplicons of less than approximately 100 to 300 cannot or should not be used. There is also no indication in the specification as to what is encompassed by "approximately" such that it would be readily apparent that amplicons of "approximately 100 bases" specifically exclude amplicons of 90 bases.

Further, the cited teachings of Metallinos, Matsuzaki and Lopez each indicate that shorter amplicons were in fact conventional in the prior art. In particular, Metallinos teaches allele specific PCR to produce amplicons of 90 bp, and Matsuzaki exemplifies methods of PCR to produce amplicons of 90 bp. Lopez also teaches PCR methods to produce amplicons of 30 to 100 bp. Additionally, Matsuzaki provides the motivation to generate amplicons of shorter lengths in that Matsuzaki teaches that “(t)he yield of longer amplicons is often less than the yield of shorter amplicons because of the differences in PCR amplification efficiency (col. 1). Lopez also teaches

that shorter amplicons are produced more efficiently. Accordingly, modification of the method of Nazarenko so as to have selected primers that produced amplicons of a length less than 101 bp, and particularly that produced amplicons of a length of 90 or fewer bp, would have been obvious to one of ordinary skill in the art at the time the invention was made in order to have improved the efficiency of PCR and to have increased the yield of the target amplification product.

Conclusion

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Carla Myers whose telephone number is 571-272-0747. The examiner can normally be reached on Monday-Thursday (6:30-5:00).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ram Shukla can be reached on 571-272-0735. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Carla Myers/

Primary Examiner, Art Unit 1634